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XLMR Genes: Update 1996

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A current list of all known forms of X-linked mental retardation (XLMR) and a slightly revised classification are presented. The number of known disorders has not increased because 6 disorders have been combined based on new molecular data or on clinical grounds and only 6 newly described XLMR disorders have been reported. Of the current 105 XLMR disorders, 34 have been mapped, and 18 disorders and 1 nonspecific XLMR (FRAXE) have been cloned. The number of families with nonspecific XLMR with a LOD score of ≥2.0 has more than doubled, with 42 (including FRAXE) now being known.

A summary of the localization of presumed nonspecific mental retardation (MR) genes from well-studied X-chromosomal translocations and deletions is also included. Only 10–12 nonoverlapping loci are required to explain all localizations of nonspecific MR from both approaches.

These new trends mark the beginning of a significantly improved understanding of the role of genes on the X chromosome in producing MR. Continued close collaboration between clinical and molecular investigators will be required to complete the process.

KEY WORDS: X-linked mental retardation, review, X chromosome

INTRODUCTION

The compilation of disorders with mental retardation resulting from mutation of genes on the human X chromosome continues to change, and in this report new directions are also evident. The present summary serves as a quick reference to current reports of the 105 disorders and the 42 nonspecific X-linked mental retardation (XLMR) families included in this review. The number of new disorders is no longer increasing rapidly, and the results of more precise molecular studies are now changing the clinical views of many disorders. The most rapid increase in known localizations has occurred in relation to nonspecific XLMR. The large proportion of papers on XLMR that cite this series of updates testifies to the usefulness of these biannual reviews and compilations.

METHODS

A slightly revised arrangement of the previous classification [62] is presented in Table I. Essentially the same groups are used, but they are subdivided into 3 main categories: X-linked recessive and partly dominant disorders (including syndromes, neuromuscular disorders, and metabolic disorders), dominant lethal disorders, and nonspecific XLMR. This classification is more consistent with the genetic origin of the group of disorders.

Although our collective experience was the primary source of information, considerable help was gained from the increasingly accessible and up-to-date OMIM listings [66]. We have tried to correlate our listings with MIM and OMIM listings, but a number of inconsistencies in the MIM catalog such as the continued inclusion of some specific disorders in the nonspecific XLMR listing (MIM 309530) make this difficult, and some inconsistencies will certainly persist. Some clinical reviewers, for example, will elect to "lump" 2 disorders that other reviewers might "split." With the increasing lumping of disorders from cloning and molecular studies, some inevitable inconsistency will persist as to whether 2 allelic disorders that are clinically disparate should retain individual clinical listings or be listed simply as allelic variants. In the case of the Pelizaeus–Merzbacher syndrome, for example, the clinical disorders resulting from mutations at this locus seemed to be sufficiently similar to be listed as allelic variants without separate disease listings, even though the authors who reported spastic paraplegia as an allelic disorder reached the opposite conclusion [82]. Disorders such as X-linked spinal muscular atrophy and

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TABLE I. Changes in Localization and Cloning of XLMR Conditions

	Number		Gene cloned		Gene mapped	
Class	1994	1996	1994	1996	1994	1996
Recessive disorders[a]						
Syndromes	57	56	1	4	21	18
Metabolic	12	13	9	10	0	1
Neuromuscular disorders	30	30	4	4	10	11
Dominant lethal disorders	6	6	0	0	4	4
Total disorders	105	105	14	18	35	34
Nonspecific XLMR	22	42[b]	1	1	18	42[b]
Total entries	127	147[b]	15	19	53	76[b]

[a]Includes semidominant disorders and those with frequent manifestations in females.
[b]Includes 41 XLMR families, with LOD ≥2 (published or numbered) and FRAXE.

testicular feminization (which is not associated with mental retardation) are so distinct, albeit allelic, that separate clinical listings seem justified.

The localizations shown in the X-chromosome maps have been revised to include the most recently available data, and the number of disorders listed has been updated after the various lumpings and splittings referred to in the text. A complete list of all published or in-press XLMR families is included. We have included only nonspecific families that have been given an XLMR number and have a LOD score of ≥2.0 because of the large number of reported families with significant LOD scores. Throughout the paper, we have listed only recent references that are not included in the OMIM listing or are critical to the text.

RESULTS

A summary of the 105 known disorders and 42 XLMR families is given in Table I, and a detailed current list of disorders in each of the categories is provided in Tables II–VI. A revised map of cloned and localized disorders is shown in Fig. 1. The details of these revisions are discussed in the text and are compared with the results of previous updates [62–64].

New Entries, Localizations, and Deletions of Entries

Three new syndromes are included (Table II). One was localized and 2 had possible localizations. Aldred et al. [1] described a kindred with mental retardation (MR), retinitis pigmentosa, and microcephaly in some cases. The linkage data suggested a localization to Xp21–q21 but did not reach significance.

Wittwer et al. [103] described a syndrome that includes a square face, high broad forehead, frontal bossing, downslanting palpebral fissures, hypertelorism, epicanthic folds, long philtrum, and thin upper lip. Three affected males were blind due to microphthalmos, sclerocornea, or optic nerve atrophy. A variety of other findings was described. The linkage data suggested localization to Xp22.3 but did not reach significance.

Opitz GBBB syndrome (MIM145410) is heterogeneous [75], with an X-linked and an autosomal form. In 6 families with no male-to-male transmission, a Z_{max} of 3.87 ($\Theta = 0.0$) was obtained with DXS987 (Xp22). No clinical differences were noted between these families and those localizing to 22q11.2. One syndrome,

TABLE II. XLMR Syndromes[a]

MIM no.	Syndrome	Locus	Description
*305400	Aarskog–Scott (FGDY)	Xp11.22[b]	Hypertelorism, short stature, downslanting palpebral fissures, anteverted nostrils, shawl scrotum, joint hyperlaxity
304200	Åkesson		Cutis verticis gyrata, thyroid aplasia
*301040	α-thalassemia with MR (ATR-X)	Xq13.3[b]	Microcephaly, "coarse" face, genital and skeletal abnormalities, HbH, inclusions in some; includes Juberg–Marsidi (309590)
*301900	Börjeson–Forssman–Lehman	Xq26-q27	Obesity, hypogonadism, round face, narrow palpebral fissures, epilepsy
301950	Branchial arch		Short stature, downslanting eyes, lowset ears, highly arched palate, webbed neck
308830	Cantú		Macrocephaly, dwarfism, keratosis follicularis
*303600	Coffin–Lowry	Xp22.2–p22.1	"Coarse face," drumstick phalanges, skeletal anomalies
*309620	Christian	Xq27-q28	Skeletal dysplasia, sixth nerve palsy
309490	Chudley–Lowry		Short stature, obesity, small genitalia
*305000	Dyskeratosis congenita	Xq28	Skin pigmentation, nail dystrophy, leukoplakia of oral mucosa
*305450	FG (Opitz-Kaveggia) [8]		Macrocephaly, agenesis of corpus callosum, gastrointestinal anomalies, deafness
*309550	Fragile X	Xq27.3[b]	Macrocephaly, long face, long ears, macroorchidism
*301590	Graham		Anophthalmos, ankyloblepharon, orbital underdevelopment
*302000	Hereditary bullous dysfunction [77, 100]	Xq26–q28	Short stature, microcephaly, alopecia, bullous dystrophy, hypogenitalism

TABLE II. XLMR Syndromes[a] (*Continued*)

MIM no.	Syndrome	Locus	Description
307010	Hydrocephalus with cerebellar agenesis		Hydrocephalus, cerebellar agenesis, absence of foramina of Magendie and Luschka
*309800	Lenz		Microphthalmia, thumb and skeletal anomalies, urogenital and cardiovascular malformations
*309520	Lujan–Fryns		Marfanoid habitus, triangular face, narrow palate, hypernasal voice
*309605	Miles (MRXS4)	Xp21.1–q22	Microcephaly, asymmetric face, hypogonadism, joint hypermobility, 10 digital arches
*302350	Nance–Horan	Xp22.3-p21.1	Cataract, microcornea, cone-shaped incisors, supernumerary teeth
300000	Opitz GBBB [76]	Xp22	Hypertelorism, hypospadias
*311300	Otopalato-digital	Xq27–q28	Short stature, hearing loss, cleft palate, characteristic face
*309510	Partington (MRXS1)	Xp22.1–p21.3	Dysarthria, dystonic movements of hands, ataxia, seizures
*304340	Pettigrew (MRXS5)	Xq26–q27.1	Long "coarse" face, hydrocephalus, hypotonia, spasticity, ataxia, seizures, iron accumulation in basal ganglia, Dandy Walker
*309610	Prieto (MRXS2)	Xp21.1–p11.22	Peculiar face, dental anomalies, sacral dimple, joint dysplasia, epilepsy
*309500	Renpenning [85]	Xp21.1–q12	Microcephaly, short stature
308200	Rud	Xp22	Ichthyosis, epilepsy, nystagmus, hypogonadism
314320	Say–Meyer		Trigonocephaly, short stature
*312870	Simpson–Golabi–Behmel (SGB)	Xq24–q28[b]	Macrosomia, "coarse" face, polydactyly, extra nipples, heart defect
309580	Smith-Fineman Myers		Peculiar face, microcephaly, short stature, seizures
*309583	Snyder–Robinson [2]	Xp22.3–p21.3	Macrocephaly, long thin face, high narrow/cleft palate, asthenic body build, scoliosis
*309470	Sutherland (MRXS3) [20]	Xp21.1–q22	Microcephaly, short stature, small testes, spastic diplegia
309480	Tranebjaerg I		Epilepsy, psoriasis
314390	VACTERL with hydrocephalus [25]		Vertebral, anal, tracheo-esophageal renal, and radial defects, plus hydrocephaly
*314500	van den Bosch		Choroideremia, acrokeratosis verruciformis, anhydrosis, skeletal deformities
311450	W syndrome		Characteristic face, clefting, subluxed elbow, camptodactyly
308400	Warkany		Intrauterine growth retardation, microcephaly
*309585	Wilson (MRXS6)	Xp21.1–q22	Obesity, gynecomastia, tapering fingers, emotional lability
600100	Zollino [6, 105]		Peculiar face, micropenis, micrognathia, failure to thrive, hypotonia and seizures, lissencephaly and agenesis of corpus callosum, includes Berry-Krevis.
	Aldred [1]		Retinitis pigmentosa, microcephaly
	Atkin–Flaitz [4]		Macrocephaly, "coarse" face, short stature, macroorchidism
	Brooks [9, 61]		Peculiar face, growth retardation, optic atrophy, spastic diplegia, atrophic hydrocephalus
	Carpenter [10]		Peculiar face, brachydactyly, short stature
	Golabi–Ito–Hall [28]		Short stature, triangular face, epicanthic folds, microcephaly, brittle hair
	Hamel [35]		Congenital heart defect, cleft palate, short stature, facial anomalies
	Holmes–Gang [42]		"Coarse" face, epicanthic folds, flat nasal bridge, dental anomalies
	Hyde–Forster [44]		Craniofacial anomalies with plagiocephaly, flattened occiput
	Kang [49]		Microcephaly, dysagenesis of corpus callosum, hydrocephalus, spasticity, short broad hands, facial anomalies
	Porteous [71]	Xp11.4–q13	Short stature, high-pitched voice, high forehead, receding hairline
	Proud [72]		Microcephaly, agenesis of corpus callosum, arthrogryposis, renal dysplasia, hypospadias
	Stocco dos Santos [87]		Short stature, hip luxation, precocius puberty
	Stoll [88]		Short stature, prominent forehead, hypertelorism, broad nasal tip, anterveted nares
	Tariverdian [91]		Acromegaly, central nervous system anomalies, macroorchidism
	Vasquez [96]		Hypogonadism, gynecomastia, short stature, obesity
	Vles [99]		Corpus callosum agenesis, spastic quadriparesis, irregular lining of lateral ventricles
	Wittwer [103]		Square face, high broad forehead, frontal bossing, downslanting palpebral fissures, hypertelorism, anteverted nares
	Young–Hughes [104]		Short stature, obesity, hypogonadism

[a]References are given only when an MIM number has not been assigned or if a reference is new. Asterisk indicates mode of inheritance established and phenotype determined by gene at a locus separate from other asterisked entries in MIM.
[b]Cloned gene.

TABLE III. XLMR Dominant Syndromes Lethal in Males

MIM no.	Syndrome	Locus	Description
304050	Aicardi	Xp22	Agenesis of corpus callosum, chorioretinopathy, microphthalmia, seizures
*305600	Goltz		Focal dermal hypoplasia, short missing digits, polysyndactyly, microphthalmia
*308310	Incontinentia pigmentii	Xq28	Incontinentia pigmenti, incomplete dentition, retinal abnormalities
	MIDAS [38]	Xp22	Microphthalmia, dermal aplasia, sclerocornea
*311200	OFD-I		Midline clefting of face, tongue nodules, syndactyly
312750	Rett	Xp21–p11	Ataxia, autism, dementia

spondylometaphyseal dysplasia (MIM313420), has been deleted.

Two new metabolic disorders have been added (Table IV). The gene for phosphoglycerate kinase (PGK1, MIM311800) was previously cloned. The gene has been associated primarily with hemolytic anemia. However, in 1989, Sugie et al. [89] reported on 3 unrelated men who presented with myoglobinuria; the men were mentally retarded, 2 had epilepsy, and 1 had hemolytic anemia. Sugie et al. postulated that the mental deficiency resulted directly from the presumed mutations rather than being secondary to the hemolytic anemia. Other explanations, including an unidentified contiguous gene syndrome, might explain these observations; additional studies will be needed for this type of XLMR to be completely understood. This entity is only now being entered into the listing.

Hamel et al. [34] reported a new XLMR syndrome associated with decreased stature and isolated growth hormone deficiency, but with no other clinical findings except a small sella turcica and pituitary. Growth continued into the subject's 20s.

Concomitantly, glutaric aciduria (MIM305950) was deleted from the MIM listing because of lack of evidence for an X-linked form, and we have also deleted this metabolic disorder from our list. Thus, the total number of metabolic disorders leading to XLMR has increased by 1.

Myotubular myopathy (MTM, MIM310400), which was localized to Xq28 near L1CAM, has been added to the list of neuromuscular disorders (Table V). Although MR has been assumed to be likely, more direct evidence indicates a developmental delay among the older survivors. A second locus was postulated by Samson et al. [80] because 1 family was not linked. The previously separate listing of Berry-Krevis syndrome has now been included with Zollino syndrome, and the number of neuromuscular disorders is unchanged.

New Clonings

Genes for 3 XLMR disorders, Aarskog–Scott syndrome [68], Simpson–Golabi–Behmel (SGB) syndrome [70], and α-thalassemia with MR [26] have been cloned since the last report. PGK1, which had previously been cloned, has now been added to the list of XLMR disorders. This addition brings the total number of cloned disorders to 19. The report by Pasteris et al. [68], which stated that the gene for Aarskog–Scott

TABLE IV. XLMR Metabolic Disorders

MIM no.	Syndrome	Locus	Description
*300100	ALD	Xq28[a]	Spastic quadriparesis, impaired vision, ataxia, dementia
300800	Albright hereditary osteodystrophy		Short stature, brachydactyly, subcutaneous calcifications, muscular atrophy
*309850	MAO-A deficiency	Xp11.4–p11.23[a]	Aggressive and violent behavior, disturbance in monoamine metabolism
305650	GM3 gangliosidosis		"Coarse" face, macroglossia, stubby hands and feet, inguinal hernias
*307030	Glycerol kinase deficiency [32]	Xp21.3-2[a]	Glyceroluria, poor growth, esotropia, osteoporosis
*309900	Hunter syndrome	Xq27.3-q28[a]	"Coarse" face, dysostosis multiplex, dwarfism, hepatosplenomegaly, heart involvement
*308000	Lesch–Nyhan	Xq26.1[a]	Cerebral palsy, choreoathetosis, self-destructive biting
*309000	Lowe	Xq25-q26.1[a]	Hydrophthalmia, cataract, vitamin-D-resistant rickets
*309400	Menkes	Xq13.3[a]	Growth retardation, peculiar hair, focal cerebral and cerebellar degeneration, includes 304150 (occipital horn syndrome or cutis laxa), which is allelic
*311250	OTC deficiency	Xp21.1[a]	Hyperammonemia
311800	Phosphoglycerate kinase defeciency (PGK1) [89]	Xq21.1[a]	Myoglobinuria, epilepsy, 1 of 3 with hemolytic anemia
*312170	Pyruvate dehydrogenase deficiency	Xp22.2–p22.1[a]	Lactic acidosis, ataxia
	Growth hormone deficiency [36]	Xq24–q27.3	Short stature, small sella turcica

[a]Cloned gene.

TABLE V. XLMR Neuromuscular Disorders

MIM no.	Syndrome	Locus	Description
*309600	Allan–Herndon–Dudley	Xp11.4–q21.3	Severe hypotonia, joint contractures, muscular atrophy
*302500	Apak		Spinocerebellar ataxia, nystagmus, dysarthria
301835	Arts		Early death, hypotonia, ataxia, deafness, loss of vision, recurrent infections
301840	Ataxia–dementia		Ataxia, pyramidal tract signs, adult-onset dementia
312890	Baar–Gabriel		Spastic athetotic paraplegia
309660	Bergia		Cardiomyopathy, scapuloperoneal muscular dystrophy, myopia
310490	Cowchock–Fishbeck	Xq13–q21	Motor–sensory neuropathy, deafness
*310200	Duchenne muscular dystrophy	Xp21.3-1[a]	Pseudohypertrophic muscular dystrophy
309560	Fitzsimmons		Diplegia, pes cavus, palmoplantar hyperkeratosis
*312920	Goldblatt	Xq13–q21.1	Spastic paraplegia, nystagmus, optic atrophy
311150	Jensen		Opticoacoustic nerve atrophy, dementia
*308840	L1CAM mutations	Xq28[a]	Clasped thumb, retardation, adducted thumbs, spasticity, and hydrocephaly (formerly MASA, HSAS)
*304100	Menkes–Kaplan		Partial agenesis of corpus callosum, seizures
*304700	Mohr–Tranebjaerg	Xq22	Hearing loss, visual impairment, ataxia, spastic paraplegia
310400	Myotubular myopathy [48, 80]	Xq28	Severe hypotonia, macrocephaly or hydrocephaly, birth length in >90th centile, long narrow face and fingers, cryptorchidism
*310600	Norrie	Xp11.3[a]	Blindness, hearing loss
*311050	OPA-2		Optic atrophy, abnormal reflexes, dysarthria, tremor
311400	Paine–Seemanová		Spastic diplegia, myoclonic seizures, cerebellar hypoplasia
*312080	Pelizaeus–Merzbacher	Xq21.33–q22[a]	Spasticity, cerebellar ataxia, parkinsonism (includes spastic paraplegia II)
308850	Plott		Laryngeal abductor paralysis
301790	Schmidley		Hypotonia, ataxia, sensorineural deafness, optic atrophy
*311510	Waisman–Laxova	Xq27.2–q28	Parkinsonism, seizures, apparent basal ganglia degeneration
311050	Went		Optic atrophy, dysarthria, tremor, dysdiadochokinesis
*314580	Wieacker–Wolff	Xq11–q22	Contractures, distal muscular atrophy, dyspraxia of ocular and facial muscles
	Arena [3]		Spastic paraplegia, ataxia, titubation, iron deposits in basal ganglia
	Bertini [7, 14]	Xq22.33-pter	Ataxia, hypotonia, recurrent infections
	Gustavson [33]	Xq25–q26	Optic atrophy, hearing loss, epilepsy, spasticity, restricted joint mobility, early death
	Ionasescu [46]	Xp22.3-1	Motor–sensory neuropathy
	Passos–Bueno [67]	Xp21.2–q21.31	Hypotonicity, incontinence, severe generalized muscle atrophy
	Tranebjaerg II [93]		Dyspraxia, ataxia, seizures, pes equinovarus, macroorchidism

[a]Cloned gene.

syndrome (faciogenital dysplasia) was due to a Rho-Rac guanine nucleotide exchange factor, was based on molecular studies in a previously reported patient with Aarskog–Scott syndrome and an X-chromosome translocation. This important work will permit the study of mechanisms by which the many clinical findings and variable MR develop. Because this syndrome was originally reported independently at the same meeting by Aarskog and by Scott, it is more appropriately referred to as Aarskog–Scott syndrome than as Aarskog syndrome.

The gene for SGB overgrowth syndrome, a glypican gene, was cloned by Pilia et al. [70]. Further clarification of the clinical findings will presumably follow.

The initial report by Gibbons et al. [26] that a form of α-thalassemia (ATR-X) was both X-linked and associated with MR was an unexpected observation. The locus is in Xq13.3, and the gene, which is in the helicase family, is possibly a global transcription regulator. This cloning was accomplished through a search for an appropriate candidate gene in Xq13. Because the gene is also expressed in the urogenital tract and patients have urogenital abnormalities in addition to MR, the scope of this disorder should expand in the near future, and (see Juberg–Marsidi syndrome in the following section) other XLMR syndromes localized to this region may also prove to be allelic. Mutations at this locus may also result in nonspecific XLMR, and studies need to be done to investigate this possibility. As in a number of other XLMR disorders, carriers have highly skewed X inactivation; the locus is just distal to XIST.

FRAXE was listed prematurely as cloned in the previous update based on the report by Knight et al. [51]. Three reports [11, 19, 31] have provided more definitive sequence information but have not completely resolved the complex relations in this region because the sequence provided by Chakrabarti et al. [11] differed from that provided by Gecz et al. [19] and by Gu et al. [31] and was shorter.

New Lumpings

Continued studies in 2 previously cloned disorders have now demonstrated multiple instances of allelism for each locus and have permitted the lumping of a number of disorders previously thought to be discrete entities. Juberg–Marsidi syndrome (MIM309590) is an

TABLE VI. XLMR Nonspecific MRX Forms

Reference	Name	Locus	Description
Suthers et al. [90]	MRX1	Xp11.3–q12	MR only
Hu et al. [45]	MRX2	Xp22.2–p21.3	Macrocephaly, square face, macroorchidism, short stature heterozygote manifestation
Gedeon et al. [23]	MR3	Xq28	Mild–moderate MR, behavior problems, brachycephaly, increased limb span
Hu et al. [45]	MRX4	Xp11.23–q21.31	Speech delay, learning disability
Samanns et al. [79]	MRX5	Xp11.4–q21.2	Hyperactive behavior, speech delay
Kondo et al. [52]	MRX6	Xq27	Short stature, "coarse face," short broad hands and feet, heterozygote manifestation
Jedele et al. [47]	MRX7	Xp11.4–q21.32	MR only
Schwartz et al. [86]	MRX8	Xp11.3–q21.33	MR only
Willems et al. [101]	MRX9	Xp21.1–q12	MR only
Gedeon et al. [22]	MRX10	Xp21.3–p11.4	Hypotelorism, large ears, heterozygote manifestation
Gedeon et al. [22]	MRX11	Xp21.1–p11.4	Hypotelorism, large ears, heterozygote manifestation
Gedeon et al. [22]	MRX12	Xp21.2–q11.21	Hypotelorism, large ears, prematurity/low birth weight, short stature
Kerr et al. [50]	MRX13	Xp21.22–q22.3	Large ears
Gendrot et al. [24]	MRX14	Xp11.3–q13.2	Inconsistent phenotypic abnormalities
Raynaud et al. [74]	MRX15	Xp21.1–p11.2	Congenital hypotonia, delayed or absent speech, thin habitus, scoliosis
Moraine et al. [60]	MRX16	Xq28-qter	
Gedeon et al. [22]	MRX17	Xp11.23–q12	MR only
Gedeon et al. [22]	MRX18	Xp21–p11.23	MR only
Donnelly et al. [16]	MRX19	Xp22.31–p22.13	MR only
Lazzarini et al. [56]	MRX20	Xq21	MR only
Kozak et al. [53]	MRX21	Xpter-p11.4	MR only, heterozygote manifestation
Passos-Bueno et al. [67]	MRX22	Xp21.1–q21.31	Generalized muscle atrophy
Gregg et al. [29]	MRX23	Xq23–q24	Not available
Martínez et al. [58]	MRX24	Xp22.32–p22.2	"Slightly coarse facies," small head circumference
Nordström et al. [65]	MRX25	Xq27.3-qter	MR only, heterozygote manifestation
Robledo et al. [76]	MRX26	Xp11.3–q21.33	MR only
Gedeon et al. [21]	MRX27	Xq23–q26.3	Growth failure, mutism, seizures, brachycephaly, square face
Holinski-Feder et al. [40, 41]	MRX28	Xq28	Moderate MR
Hane et al. [37]	MRX29	Xp22.2–p21.1	Severe MR
Donnelly et al. [15]	MRX30	Xq21.33–q23	Mild MR
Donnelly et al. [15]	MRX31	Xp11.23–q13	Moderate MR
Hane et al. [37]	MRX32	Xq21.2–p22.1	Variable MR
Holinski-Feders et al. [40, 41]	MRX33	Xp22.12–Xp11.4	Moderate MR
Raeymaekers et al. [73]	MRX34	Xp21.3–Xp22.1	Moderate–mild MR, heterozygote manifestation
Gu et al. [30]	MRX35	Xq22–Xq26	Moderate MR, heterozygote manifestation
Claes et al. [12]	MRX36	Xp22.1–Xp21.2	Moderate MR
Bar-David et al. [5]	MRX37	Xp22.32–Xp22.31	Moderate MR
Schutz et al. [84]	MRX38	Xp21.1–Xp22.13	Macrocephaly, seizures
Philippe et al. [69], Teboul et al. [92]	MRX39		
	MRX40		Not available
Hamel et al. [34]	MRX41	Xq28	Mild or moderate MR
Charkrabarti et al. [11], Gecz et al. [19], Gu etal. [31], Knight et al. [51]	FRAXE	Xq28[a]	Mild MR

[a]Cloned gene.

allelic variant of ATR-X, as demonstrated by Villard et al. [97, 98], which followed the localization to Xq12–q21 by Saugier-Veber et al. [81]. Classic X-linked hydrocephalus, HSAS, MASA, spastic paraplegia, clasped thumb, and a form of agenesis of the corpus callosum, have all been shown to be secondary to mutations in L1CAM (MIM308840). HSAS and MASA were previously listed as separate entities and are now both included as L1CAM mutations. No clear clinical–specific mutation correlations have evolved; as with α-thalassemia, nonspecific XLMR may also be a clinical manifestation of mutation at this locus [17].

Similarly, additional clinical disorders associated with mutations at the Pelizaeus–Merzbacher locus continue to be reported, and the clinical spectrum of this disorder also appears likely to broaden. Spastic paraplegia 2, for example, is due to mutation at the same locus, as deomonstrated by Saugier-Veber et al. [82]. (This report does not change the number of disorders because it was not listed as a separate disorder 2 years ago.)

Several other developments deserve comment. The current MIM600102 (lissencephaly and agenesis of the corpus callosum), which was reported by Berry-Krevis

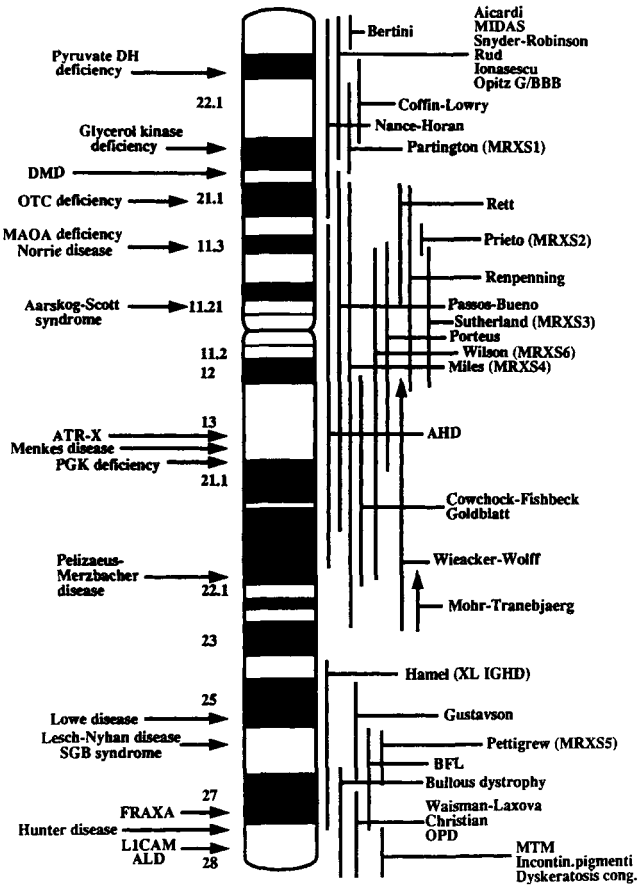

Fig. 1. Map of XLMR conditions. Cloned genes are shown by an arrow on the left. ATR-X, Aarskog–Scott, PGK, and SGB have been added since 1994. One new localization is shown for Opitz, and localizations have been narrowed for Prieto [57], bullous dystrophy [100], and Sutherland [20] (on right). Localizations of the top 6 syndromes on the right (Aicardi–Opitz) are presented by one line for simplicity but are not precisely the same because of different markers, etc.

et al. [6] and is included in the 1994 update, is clearly the same syndrome listed in the previous update as Zollinoet et al. [105]. Although the MIM listing does not include Zollino et al. [105] as a reference, we have included both entities in the current list of syndromes under lissencephaly. The syndrome previously listed under Cowles et al. [13] has been included in the MIM listings under the Pettigrew syndrome (MIM304340) because of the clinical similarity, although there are no localization data to support this lumping.

Summary of Changes in the Number of XLMR Disorders

In summary, 6 new disorders have been included (PGK-1, XLMR with growth hormone deficiency, myotubular myopathy, and the Aldred, Wittwer, and Opitz Syndromes). Two (GK and spondylometaphyseal dysplasia) were deleted. However, pooling of Berry-Krevis and Zollino syndromes and the Cowles and Pettigrew syndromes further decreases the number by 2. In addition, Juberg–Marsidi was allelic to ATR-X, and HSAS and MASA are allelic variants of L1CAM. Thus, the gain of 6 listings was offset by "pooling" in 6 instances and the overall number of disorders has not changed.

Other Disorders

A possible localization of the FG ("Opitz–Kaveggia") syndrome to Xq was reported by Briault et al. [8] in a family in whom a large Xq paracentric inversion was segregating with this disorder. DesPortes et al. [14] restudied the family reported by Bertini et al. [7] and localized the gene to Xq22.33.

Craniofrontonasal dysplasia (MIM304120) was considered a possible new XLMR disorder. Because of a number of uncertain aspects, including the absence of clear proof that it is indeed an X-linked dominant disorder, a 4:1 female:male ratio, the finding that females are more severely affected than males, and the presence of only a borderline IQ in 3 individuals (81, 65, and 71) [54], we have elected not to include it in this listing. However, we wish to call attention to this disorder, so that more information may be gained about this possible XLMR disorder.

The current MIM includes 2 families with hypogonadism, short stature, and MR under 309585. These 2 families, reported by Vasquez et al. [96] and Wilson et al. [102], are sufficiently different in their clinical findings in their limb and behavior aspects that separate listings are continued here.

A MIM number (314360) now exists for VACTERL-H with hydrocephalus, although the initial report by Genuardi et al. [25] (included in our last update) was not cited in the MIM listing. Our current listing adopts the MIM designation, with reference to this earlier report [25].

Nonspecific XLMR

Forty-one XLMR families with a LOD score of ≥ 2.0 have now been given a genome designation and are summarized in Table VI. The family with a LOD score of <2 reported by Glass et al. [27] was restudied and designated as MRX27. The family reported by Howard-Peebles et al. [43] has also been restudied and designated MRX32. In the 1994 compilation, 22 XLMR families were listed; However, these included families with LOD scores of <2 and those with a LOD score of ≥ 2. Thus, although the present listing is more rigorous, it still reflects a significantly larger number of families. FRAXE, the first gene for nonspecific XLMR to be cloned, is discussed in that section.

A detailed analysis of the limiting markers in 32 of these families was presented by Gedeon et al. [22]. They clearly demonstrated through a careful review of earlier reports and a restudy of several previously reported families that only 8 nonoverlapping regions derived from these data would be required to account for all 32 MRX entries (Fig. 2). (MRX33–41 have been assigned since the completion of that detailed map and are not included in this summary map.) This number remains minimal because more nonoverlapping localizations may be described, and each of the 32 XLMR families must be considered as being potentially due to

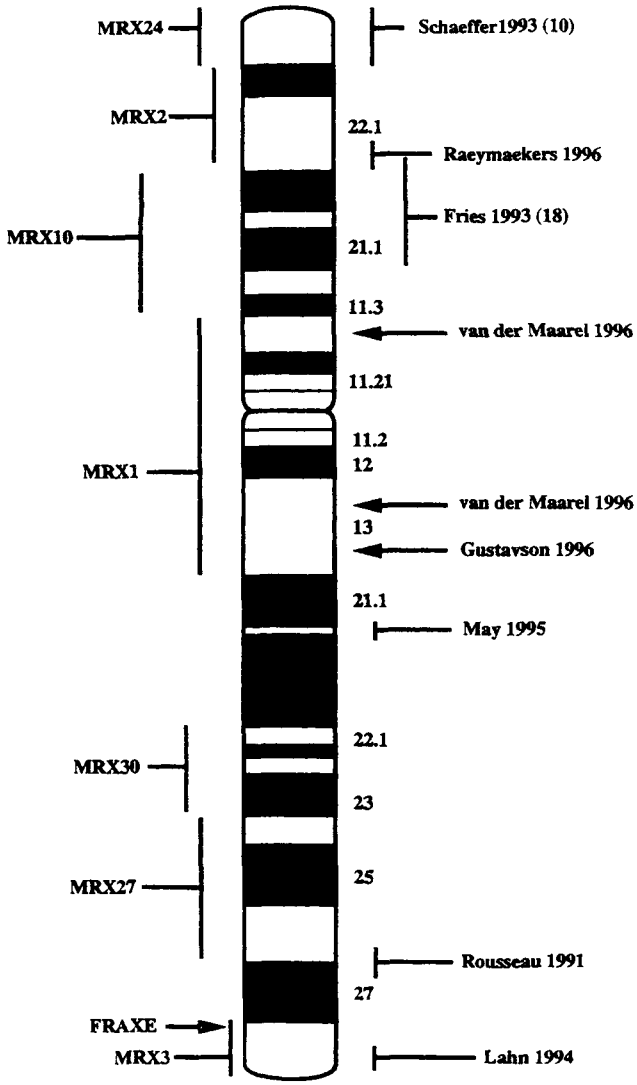

Fig. 2. Map of nonspecific XLMR. The minimal number of (nonoverlapping) localizations required to account for 32 MRX localizations are shown to the left, as described by Gedeon et al. [22]. To the right are shown the results of recent molecular studies that have localized presumed genes for nonspecific MR from patients with structural abnormalities of the X chromosome. Complete references are in the reference list [see references 83 (top right), 73, 18, 94, 95, 33, 59, 78, 55 (bottom right)]. MRX references are given in Table VI. Where more than one individual has been studied, the number of subjects is shown in parentheses, as in Fries et al. [18] where 18 subjects with overlapping detection were analyzed. At least, 10 loci are required to account for both types of localizations.

a unique gene until detailed molecular and cloning studies have been successfully completed.

Nonspecific XLMR Genes Localized From Structural Abnormalities of the X Chromosome

A summary of possible identifications of additional genes for nonspecific XLMR resulting from studies of X-chromosomal translocation break points and deletions is also given in Figure 2. Only recent studies with molecular characterization of the break points or deletions were included. Some of these tentatively identified regions have come from studies of deletions in Xp in which MR could not be accounted for by any known disorder in the deleted region. These regions were included if they resulted from multiple, similar observations. In other cases, such as in the X-autosomal translocations studies, the results are based on only 1 carefully studied localization, and the possibility that the break point in the autosomal half of the translocalization point might be responsible for the MR cannot be excluded.

DISCUSSION

The most striking advances have been in the identification of possible genes for nonspecific XLMR. The number of reported families with a LOD score of ≥ 2 has grown from 22 to 42, and exciting progress has been reported in the identification of possible specific sites for XLMR genes from the study of X-autosomal translocations and small deletions. Although a significant overlap exists between the results of these 2 approaches, as shown in Figure 2, at least 10–12 nonoverlapping genes must be evoked to explain this group of disorders. The results of studies of structural abnormalities and the report by Raeymaekers et al. [73] of a discrete microdeletion in 1 of these families suggests that significant progress may occur in the next several years through studies of candidate genes. A more precise answer to the question of "how many genes?" posed in a previous update [62] and in the paper by Gedeon et al. [22] should follow in the next few years, and the original estimate of Herbst and Miller [39] that 7–19 loci could account for all families with nonspecific XLMR may prove to be correct.

Several other trends are clear. For the first time, the number of XLMR entities has not increased. Although 6 new disorders were described, these have been offset by combining 2 syndromes as allelic variations of previously cloned genes, Juberg–Marsidi with ATR-X and HSAS and MASA, clinical decisions to lump 2 other disorders with similar syndromes, and deletion of 2 disorders. With the expected new clonings in the next few years, the number of XLMR disorders will begin to decrease in the near future, which will result in a simpler classification and diagnostic approach. Significant progress in the development of specific molecular tests for this group of disorders will also likely continue, although some time will pass before one of the clinical goals in this group of studies will be achieved, namely a battery of molecular tests that can be employed to make a precise diagnosis in a male with possible XLMR.

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